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Abstract: The microwave-assisted synthesis of terminal α-hydroxy ketones from acid chlorides and tris(trimethylsiloxy)ethylene in the presence of triethylamine is reported. The use of triethylamine had several advantages in the reaction: it increased the reactivity of the acid chloride, acted as a scavenger of the HCl that was produced in the reaction, protected the silylated enol from decomposition, and made the excess use of the silyl reagent unnecessary. Mechanistic effects of triethylamine are discussed. Effects of various base additives, reaction temperatures, reaction times, and solvents in the reaction are compared.

Keywords: α-Hydroxy ketone, hydroxymethyl ketone, microwave-assisted synthesis, Wissner reaction

INTRODUCTION

Hydroxymethyl ketones are analogs of dihydroxyacetone, a compound that widely occurs in natural products and participates in biological processes.[1] α-Hydroxy substituted ketones are conventionally produced by catalytic[2] or stoichiometric[3] oxidation of terminal olefins. 1,2-Disubstituted diols[4–6] or α-halo substituted ketones[7] can also be selectively converted to terminal α-hydroxy ketones. In some cases, the oxidation of oxirane with dimethylsulfoxide[8] or kinetically controlled

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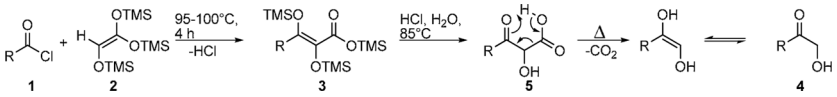


Scheme 1. Wissner hydroxy ketone synthesis, a modification of Mukaiyama's aldol reaction.[13]

α-hydroxylation of ketones[9] can be used to synthesize the α-hydroxy ketone functionality.

Cross condensation is generally used to extend the carbon chain by two or more carbon atoms, but in the reaction with diazomethane[10] or paraformaldehyde[11] the one-carbon chain extension can also be achieved. However, these reagents are hazardous and difficult to handle, particularly in a large-scale reaction or a closed microwave reactor. The Wissner modification of Mukaiyama's[12] aldol reaction lengthens the carbon chain by one carbon atom. The acid chloride **1** and the silylated ketene acetal **2**[13,14] were presented to generate a β-enol ester **3**, which decarboxylated to the product **4** (Scheme 1).[15]

Here we report our modification of this condensation reaction and its application for the preparation of some substituted hydroxymethyl ketones **4** using microwave heating. We show that the use of triethylamine in this reaction increases the reactivity of the carboxyl compound **1** and protects tris(trimethylsiloxy)ethylene (**2**) from decomposition.

RESULTS AND DISCUSSION

The Wissner hydroxy ketone synthesis[16] is sensitive to moisture. It also needs either heating or the assistance of a Lewis acid to be completed.[15] The original reaction requires 2 equiv. of enol **2**. One equiv. of **2** makes a nucleophilic attack to acid chloride **1**, and the second equiv. is consumed by the HCl that evolved in the nucleophilic substitution. Finally, the formed silyl enolate **3** was subsequently hydrolyzed to β-keto acid **5**, which after decarboxylation tautomerized to the desired α-hydroxy ketone **4** (Scheme 1).[15]

During our studies, we observed that an increase in the reaction temperature clearly greater than 100°C significantly accelerated the condensation. Our experiences related to the synthetic applications of microwave activation[17] encouraged us to study the effect of microwaves on this condensation reaction. In addition, the use of the closed microwave vessel would also help avoid moisture.

The effects of reaction conditions on the condensation were studied with 1 equiv. of octanoyl chloride (**1a**) and 2.2 equiv. of tris(trimethylsiloxy)ethylene (**2**).[15] For the comparison, the mixture of the reaction

components was heated in an oil bath at 110°C for 4 h under an N_2 atmosphere. After cooling, tetrahydrofuran (THF) and 2 M HCl were successively added into the solution, which was then heated at 85°C for 30 min. According to gas chromatographic (GC) analysis, the yield of the product, 1-hydroxynonan-2-one (**4a**), was 73% (Table 1, entry 1), which was less than originally reported for **4a**.[13] In GC analysis decane was used as the internal standard. The conversion was calculated by

Table 1. Effects of variable reaction conditions and components on the reaction of octanoyl chloride (**1a**) with tris(trimethylsiloxy)ethylene (**2**)

Entry	Reaction conditions	**2** (equiv.)	Temp. (°C)	Time	Conv. of **4a**[a] (%)
1	Oil bath heating, no additives, no solvent	2.2	110	4 h	73
2	MW activation, no additives, no solvent	2.2	180	10 min	98
3	Et_3N (1.0 equiv.), THF	1.1	−10	5 min	>24[b]
4	Et_3N (1.0 equiv.), THF	1.1	rt	24 h	74
5	Et_3N (1.0 equiv.), THF	1.1	rt	72 h	76
6	MW, Et_3N (1.0 equiv.), THF	1.1	100	5 min	91
7	MW, pyridine (1.0 equiv.), THF	1.1	100	5 min	16
8	MW, 1-methylimidazole (1.0 equiv.), THF	1.1	100	5 min	—
9	MW, DIPEA (1.0 equiv.), THF	1.1	100	5 min	>50[b]
10	MW, DBU (1.0 equiv.), THF	1.1	100	5 min	—
11	MW, Et_3N (1.0 equiv.), THF	1.1	80	5 min	>79[b]
12	MW, Et_3N (1.0 equiv.), THF	1.1	120	5 min	74
13	MW, Et_3N (1.0 equiv.), THF	1.1	100	90 s[c]	>54[b]
14	MW, Et_3N (1.0 equiv.), THF	1.1	100	10 min	90
15	MW, Et_3N (1.0 equiv.), THF	1.1	100	15 min	78
16	MW, Et_3N (1.0 equiv.), toluene	1.1	100	10 min	84
17	MW, Et_3N (1.0 equiv.), CH_2Cl_2	1.1	100	5 min	67
18	MW, Et_3N (1.0 equiv.), THF	1.5	100	5 min	89
19	MW, Et_3N (2.0 equiv.), THF	1.1	100	5 min	87
20	MW, Et_3N (1.0 equiv.), THF	1.1	100	5 min	89
21	MW, Et_3N (1.0 equiv.), THF	1.1[d]	100	5 min	84

[a]Conversion of **4a** is based on the GC analysis of the reaction mixture after decarboxylation using decane as an internal standard.

[b]A part of **4a** further reacted with the octanoic acid derivative and formed 2-oxononyl octanoate as a side product (GC-MS). Look also at Ref. 25.

[c]It took 90 s to achieve the temperature of 100°C on absorption level "high" in the Biotage Initiator™ microwave reactor in a 2-mL vial.

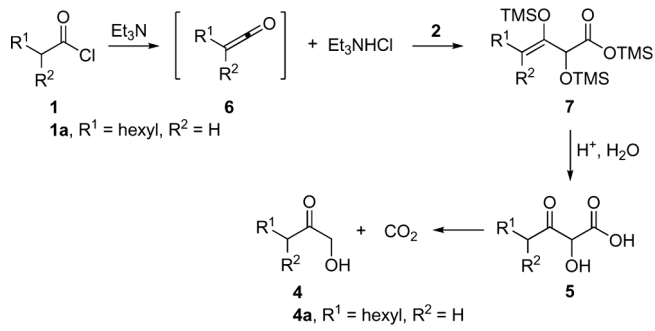
[d]Enolate **2** was added into the solution of **1a** in THF before Et_3N.

comparing the calibrated integral values of GC-signals (flame ionization detector) of decane and 1-hydroxynonan-2-one. However, when the same reaction was carried out using microwave activation (MW) at 180°C, an almost complete conversion occurred in 10 min (Table 1, entry 2).

Earlier, triethylamine had been shown to successfully accelerate the reaction of acid chloride with *O*-silyl ketene acetals.[18] Mechanistically, it is commonly approved that a tertiary amine abstracts α-proton from acid chlorides, leading to the cleavage of the chloride ion.[19] The formed ketene **6** is very reactive toward nucleophiles. We believe that the rather unstable ketene **6** in situ forms at the presence of triethylamine and directly reacts with the nucleophilic enolate **2** (Scheme 2). Besides, the Et_3NHCl by-product would increase the absorption of the microwave energy into the reaction mixture.

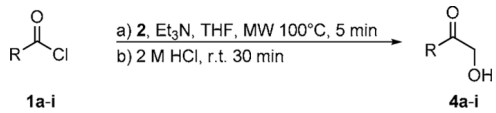
Our first experiments directly showed the benefits of triethylamine in the reaction (Table 1, entries 3–5). The base was added into the cooled mixture of octanoyl chloride (**1a**) and **2** in THF and then stirred at −10°C for 5 min. After hydrolysis and decarboxylation, the formation of **4a** was detected (entry 3). The amount of **4a** increased when the reaction was carried out at room temperature for a prolonged time (entries 4 and 5). In these reactions, the silylated β-enol ester **3** was simultaneously hydrolyzed and decarboxylated by the addition of 2 M hydrochloric acid upon heating in open vessel (80–85°C) for 30 min.[15] Later we noticed that the heating in this step was not necessary (Table 2).

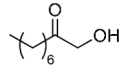
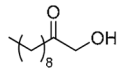
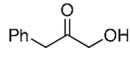
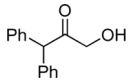
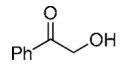
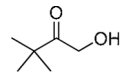
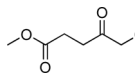
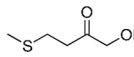
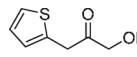
The microwave irradiation of the reaction mixture with triethylamine substantially decreased the time of condensation (entry 6). In addition to triethylamine, a set of liquid organic bases was tested at 100°C (entries 7–10). Triethylamine and diisopropylethylamine were most successful in



Scheme 2. Activating and protective effect of triethylamine in the condensation of octanoyl chloride (**1a**) with tris(trimethylsiloxy)ethylene (**2**): the formation of the ketene **6** and the capture of HCl, respectively.

Table 2. Products, yields, and reaction conditions of the microwave-assisted synthesis of terminal α-hydroxy ketones from acid chlorides **1a–i**



Entry	Product	Max. power (W)[a]	Time to reach 100°C (s)[b]	Max. press. (bar)	Continuation power (W)[c]	Yield of **4** (%)[d]	Yield in lit. (%)
1	 **4a**	250	120	1.3	60	88	84[15]
2	 **4b**	250	105	0.8	50	75[e]	—[23]
3	 **4c**	250	150	2.5	200→75	71	81[15]
4	 **4d**	220	90	1.3	100	70	—[25]
5	 **4e**	250	150	1.3	145	6 (5 min)[f] 15 (15 min)[f]	62[15]
6	 **4f**	250	>300[g]	0.4	250	—	—[26]
7	 **4g**	215	100	1.7	40	63	—[27]
8	 **4h**	250	150	0.7	120	82	—[28]
9	 **4i**	250	150	1.4	150→75	81	—

[a]The maximum microwave power that was applied to the reaction to gain the temperature of 100°C.

[b]The time needed to attain the set temperature (100°C).

[c]The microwave power required to maintain the temperature of 100°C.

[d]The yield of the isolated product. Reactions were performed on a 1-g scale in 20-mL vials.

[e]The low yield was presumable due to the poor solubility of **4b** to eluents used in purification by flash chromatography.

[f]Reaction was performed with normal procedure (5 min) and with extended microwave radiation (15 min). Conversions were estimated from ^{1}H NMR spectra of the crude product mixture (isolated only by extraction).

[g]The desired temperature was not reached during the reaction.

this reaction. Nucleophilic catalysts such as pyridine or 1-methylimidazole did not work in the reaction. When the reaction was carried out without an additional base, GC-MS analysis of the thrice-silylated β-enol α-hydroxy ester intermediate **3a** nicely fit with structure presented in the original article[15] (Table 1, entry 2). A careful study of the intermediate **7a** formed at the presence of triethylamine resulted in the same molecular mass ion as **3a** but with a slightly different fragmentation pattern (entry 6). This supports the formation of the kinetic enolate **7** and the occurrence of the reaction via ketene intermediate (Scheme 2).[18]

It was also noted that neither a cooler (80°C) nor a hotter (120°C) reaction temperature was profitable for this reaction, but the temperature of 100°C was optimal (entries 6, 11, 12). The increase of the reaction time did not improve the yield (entries 14 and 15) and neither did the use of other reaction solvents (entries 16 and 17). Toluene is a nonpolar solvent that does not absorb the microwave energy as efficiently as THF, which was seemed to slow the reaction (entry 16).[20,21] However, in toluene the cleavage of the silyl group from the carboxyl of **3** occurred to a lesser extent than in THF. The different molar ratios of the reagents or the order of their addition did not show significant effect on the yield of the product (entries 18–21).

The optimum reaction conditions found for octanoyl chloride (**1a**) were applied to reactions of **2** with variable acid chlorides **1b–i** (Table 2). The compounds **1a–f** were selected on the basis of the increasing stereochemical hindrance at the α-position (Table 2, entries 1–6), and the acid chlorides **1g–i** contained functionalities useful in our further studies related to analogs of dihydroxyacetone phosphate (entries 7–9).[23] Reactions were carried out with stoichiometric amounts of triethylamine, **1a**, and tris(trimethylsiloxy)ethylene (**2**) in dry THF under microwave heating followed by the addition of 2 M HCl solution. It was stirred for 30 min at ambient temperature. Before the microwave heating, triethylamine was added by a syringe into the reaction mixture, which turned milky white, indicating the formation of a quaternary amine **6**. Acid chlorides with a primary or secondary carbon at the α-position were also milky white mixtures after microwave irradiation and yielded α-hydroxy substituted ketones **4** in good yields (Table 2, entries 1–4 and 7–9). The more dielectric[21] reaction mixtures heated faster and required less power (entries 2, 4, and 7). The reaction mixtures were rather concentrated (1 M), and therefore their capability to absorb microwave energy was dependent on the dielectric property of the substances. The pressure in the reactor vessel followed the input power, and it was greatest when the set temperature was reached and then decreased.

A further proof of the mechanism and the presence of ketene intermediate **6** was derived from the acid chlorides **1e**,**f** without α-protons.

They did not produce white, milky mixtures as **1a–e** or **g–i** at the beginning of the reaction. Ketene did not form, and they only slightly reacted within the given reaction time (Table 2, entries 5 and 6). The yield of **4e** hardly improved by a prolongation of the reaction time (entry 5).[14] Instead, a minor amount of the product formed in the direct reaction between acid chloride **1e** and enolate **2**. In addition, the Et_3NHCl salt formed poorly, which could be seen as the low absorption of microwave energy, and therefore the direct condensation between **1f** and **2** did not take place (Table 2, entry 6). It was also detected that the cleavage and decarboxylation of the silylated intermediate **7g** could be completed without heating and even a sensitive ester group could stand the reaction conditions (entry 7).

In summary, we have presented the improved and fast synthesis for the preparation of hydroxymethyl ketones by the one-carbon chain extension using microwave heating. The use of triethylamine had several advantages: In the first step, the formation of ketene **6** from the acid chloride **1** increased the reactivity of the carbonyl group toward tris-(trimethylsiloxy)ethylene (**2**). Triethylamine protected the silyl compound **2** by neutralizing the HCl and made the excess use of **2** unnecessary. Et_3NHCl salt intensified the transfer of the microwave energy to the reaction mixture by ionic conduction. The decarboxylation could be carried out at room temperature or simply by leaving the reaction mixture to stay out overnight, which enables syntheses of labile α-hydroxy ketones. Microwave activation clearly made the condensation more effective and enables the use of short reaction times.

EXPERIMENTAL

General

Commercial reagents (Aldrich, Fluka, TCI) were purchased as 95–99% pure and used without further purification. THF was freshly distilled over metallic sodium using benzophenone indicator; pyridine was distilled over CaH and stored over molecular sieves. If necessary, petroleum ether (bp 40–65°C) was dried over 4-Å molecular sieves. Reactions were carried out in oven-dried (100°C overnight) equipment under a protective atmosphere (N_2). Microwave-assisted synthesis were performed in Biotage's Initiator^{TM} microwave reactor with a single-mode cavity in closed vials with a standard aluminum open-top seal with a septum and a Teflon-coated stirring bar. Solvents were evaporated with Büchi rotary evaporator (water aspirator) followed by the removal of trace volatiles using a vacuum oil pump. Flash chromatography was carried out using

Merck kieselgel 60 silica (230–400 mesh), and an elution was visualized by thin-layer chromatography (ultraviolet and anisaldehyde colorizing). Melting points were measured by differential scanning calorimetry on a Mettler Tolero apparatus at a heating rate of 10°C/min. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 200 spectrometer and reported in parts per million (ppm) from internal tetramethylsilane (TMS, δ_H 0.0 ppm) or $CDCl_3$ solvent (δ_C 77.16 ppm). Data are reported as follows: chemical shift [integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants, interpretation]. EI mass spectrum (GC-MS) were recorded at 70-eV ionization energies using an HP 5973 mass spectrometer and HP 6890 series GC system with DB-624 column by the Oulu University mass spectrometry laboratory. High-resolution mass spectra (HRMS) were recorded positive ($M + Na^+$) ESI by a Micromass LCT equipped with time of flight (TOF) detector *N*-(*N*-butyl)benzene-sulfonamide as a lock mass. All products were determined to be more than 95% pure by ^{1}H NMR.

General Synthetic Procedure

Acid chloride (**1a–i**, 1.0 equiv), tris(trimethylsiloxy)ethylene (**2**, 1.1 equiv),[15] and triethylamine (1.0 equiv) were successively added by a syringe into THF (1 M) in a closed reactor vessel at −10°C under an N_2 atmosphere. The reaction mixture was stirred at −10°C for an additional 5 min after which microwave power was introduced (Biotage Initiator, absorption level high, fixed hold time off, prestirring 10 s). The temperature and total irradiation time were controlled. Aqueous HCl (2 M) was added, and the reaction mixture was stirred at ambient temperature for 30 min. The water phase was saturated by NaCl and washed three times with Et_2O (**4a**,**b**,**f**,**i**) or EtOAc (**4c–e** and **4g**,**h**). The organic phases were combined, washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The product was purified by column chromatography.

The full analytical data with ^{1}H and ^{13}C NMR spectra and differential scanning calorimetry (DSC) graphs of all the compounds can be obtained by e-mail to the corresponding author.

GC-MS (EI, 70 eV) spectra of trimethylsilyl 2,3-bis(trimethylsilyloxy) dec-3-enoate (**7a**) (Table 1, entry 6); *m/z* (%) = 418 (0.5%) [M^+], 403 (3) [$M^+ - Me$], 375 (2), 328 (2), 313 (3), 301 (60) [$M^+ - COOSiMe_3$], 257 (36), 217 (7), 199 (4), 147 (45), 133 (9), 103 (8), 73 (100) [$SiMe_3^+$]. EI spectra of trimethylsilyl 2,3-bis(trimethylsilyloxy)dec-2-enoate (**3a**) (Table 1, entry 2): *m/z* (%) = 418 (16) [M^+], 403 (4) [$M^+ - Me$], 375 (4), 333 (1), 301 (22)

$[M^+ - COOSiMe_3]$, 285 (1), 244 (1), 217 (8), 147 (37), 129 (10), 103 (7), 73 (100) $[SiMe_3^+]$.

1-Hydroxy-3-(thiophen-2-yl)propan-2-one (**4i**)

Et_2O–petroleum ether, 60:40; Rf 0.31; red oil; yield 81% (0.79 g); ^1H NMR ($CDCl_3$, ppm) δ_H 7.24 (1H, dd, $J = 5.1$, 1.3 Hz, CHS), 6.98 (1H, dd, $J = 5.1$, 3.5 Hz, CHC), 6.92 (1H, m, $J = 3.5$, 1.3 Hz, SCHCHCHC), 4.34 (2H, s, $C\underline{H}_2OH$), 3.93 (2H, s, CH_2CO), 3.09 (1H, br. s, $\overline{OH}$); ^{13}C NMR δ_c 206.$\overline{2}$ (CO), 133.5 (quaternary C), 127.4, 127.3, 125.7, 67.6 (CH_2OH) 39.5 (CH_2); HRMS (ESI^+): m/z 179.0159 (calcd. 179.0143 for $C_7H_8O_2SNa$).

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